REMARKS/ARGUMENT

Status of Claims

Claims 1-15 and 17-20 and 66-89 stand rejected.

Claims 9-11, 16, 21-65, 70, 72 and 80 are canceled without prejudice.

Claim 90 stands withdrawn.

Claims 1-3, 5-8, 12-15, 17-20, 66-69, 71, 73-78, 82-87 and 89 are currently amended.

New claims 91-94 are added.

Claims 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-89 and 91-94 are currently pending.

Rejections Under 35 U.S.C. § 112, Second Paragraph.

In the Office Action, claims 1-6, 66, 67, 70, 73-76, 81 and 89 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 7-15, 17-20, 68, 71, 72, 82 and 89 are also complained of as being vague and indefinite. Additionally, claims 69, 73-78 and 83-85 are complained of as failing to relate the outcome of the final active method step with the method objective.

Claims 1, 8, 13, 14, 15, 17, 18, 19, 20, 68, 69, 73, 74, 75, 76, 82 and 83 are currently amended to more clearly link the outcome of a method step to the preamble objective. Claim 20 now provides that the presence of the estrogen binding activity indicates an anti-estrogen based therapy for treating the cancer, and an absence of the estrogen binding activity contra-indicates an anti-estrogen based therapy. This amendment is supported in Examples 19, 20, 26 and 32, paragraphs [0417], [0424], [0427], [0474], [0509], [0510], [0514], and elsewhere in the Specification.

Claims 1, 7, 8, 12, 13, 14, 17, 18, 19, 20, 68 and 71 are currently amended to omit "used" or "using," and those limitations are now rephrased.

Claim 2 is amended to improve claim form by omitting possibly redundant terms. Claim 5 has been amended to omit "substantially," in favor of claim language supported in the Specification in paragraph [0313], for example. Claim 14 has been additionally amended for better form, substituting the phrase "steroid hormone responsive normal mucosal epithelial cells" for the phrase that was objected to.

With respect to claim 15, the Office Action suggests that "[i]t is unclear how the testing of an autonomous cancer cell can aid in detecting progression to an autonomous cancer cell, as said method requires the testing of autonomous cancer cells in which the progression would already have occurred." In reply, Applicant has made a non-narrowing amendment omitting "autonomous" in steps (a) and (b),

in order to better articulate the intended steps. By testing and/or assaying a cancer cell of interest (step (a)), the presence or absence of poly-Ig receptor on the cell and its ability or inability to bind the Fc domain of dimeric/polymeric IgA or polymeric IgM (step (b)) is revealed. The absence of the receptor and/or the loss of ability to bind the Fc domain of dimeric/polymeric IgA or polymeric IgM, demonstrates that regulation of cell growth by the immunoglobulin inhibitors is not possible in that cell, and thus indicates that the cancer cell of interest has progressed from a steroid hormone responsive malignant cell to an autonomous cancer cell. Paragraph [0472] of the Specification, for instance, describes how ^{125}I-labeled IgA may be used to identify the receptor and assess its binding characteristics, as discussed in more detail below with respect to enablement.

Claim 17 is also amended to better express the intended outcome. It is now clearer that the presence of one or more of the first set of conditions indicates the presence of a cancerous or precancerous lesion in the subject, and the presence of one or more of the second set of conditions indicates an early onset cancerous or precancerous lesion. This amendment is supported in paragraph [0476].

Claim 20 is additionally amended to omit the term "high-affinity" in favor of substituting the implicit definition for that term, *i.e.*, an estrogen binding activity having a greater E_2 binding affinity than that of the well known ERα or ERβ. See paragraphs [0292] and [0363] and Example 19, entitled "A New High Estrogen Affinity Growth Regulating Estrogen Receptor (ERγ)," especially paragraphs [0411], [0416] - [0417] of the specification.

With respect to claim 70, although the phrases "form that is active for inhibiting steroid hormone responsive cancer cell growth" and "combination thereof" are well supported in the specification (see, for example paragraphs [0034], [0347], [0395], [0436] and [0605], Applicant has chosen to cancel claim 70 as being substantially duplicative of currently amended claim 1.

Claim 72 as currently amended provides for testing the Fc receptor for ability to bind IgG1. In addition to the amendment discussed above, claim 82 is further amended for improved clarity, and now omits the phrase "comparatively lower level." In this claim, it is clearer that the subject's level of dimeric/polymeric IgA and/or polymeric IgM in breast tissue is compared to that of mature adult females, as discussed in more detail below with respect to enablement of claim 82. Claim 83 has been additionally amended to omit "and/or carcinogenesis," which is said in the Office Action to be inherent in claim 82. Claim 89 is amended for clarity in accordance with the Examiner's suggested language.

Rejections Under 35 U.S.C. § 112, First Paragraph.

Written Description - Claims 8, 9-11, 13, 14, 17, 19, 67-69, 71, 72, 80 and 88.

Claims 8-11, 13, 14, 17, 19, 67-69, 71, 72, 80 and 88 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action remarks at page 11, first paragraph, that "...claims drawn to poly-Ig receptors and Fc receptors encompass defective and variant receptors which differ in amino acid sequence and function from the wild type receptors." Applicant respectfully traverses this rejection. It is important to note that claims 8, 13, 14, 17, 19, 67, 68, 69, 71, 72 and 88 are drawn to methods, not to receptors *per se*. These claims are currently amended to make explicit that which was previously implicit, *i.e.*, that cells having the detected receptor may be tested or assayed for binding or mediating activity.

More specifically, claim 8, as currently amended, recites an assay method that includes "detecting ... a receptor capable of binding the Fc domain of dimeric/polymeric IgA or polymeric IgM." To make it clearer in step (b) that an isolated Fc receptor is not required for such testing, claim 8 is also amended to recite "optionally, testing said cell for *in vitro* activity of said receptor... ." The known poly-Ig receptor on a mucosal epithelial cell is representative of any receptor that is detected according to the method. The limitation relating to binding the Fc domain of dimeric/polymeric IgA or polymeric IgM or IgG1 in claims 8, 13-15, 68, 69 and new claim 93 is supported in the Specification in one or more of paragraphs [0004], [0395], [0435], [0436] and [0453], for instance.

Claims 13, 14, 19, 68 and 69 are also amended similarly to claim 8 to better reflect that an isolated receptor is not a requirement for performing the claimed method. Claims 17, 19, 67 and 71 are currently amended to more clearly refer to the known poly-Ig receptor, Fcγ receptor, and TGFβ receptor, and their respective genes in the claimed method. Applicant's disclosure provides adequate written description of the claimed invention and is sufficient to show that one of skill in the art would conclude that Applicant was in possession of the full scope of claims 8, 13, 14, 17, 19, 67-69, 71 and 88, especially when taken in view of the general knowledge in the art.

Written Description - Claims 18, 70 and 82-85.

Claims 18, 70 and 82-85 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully submits that in claim 18, the phrase "which is in a form" is supported in the specification. For example, support is found at paragraph [0347] ("...IgA and IgM, preferably in dimeric/polymeric form, are steroid hormone reversible inhibitors of cell growth.") and paragraph [0387] ("Because IgA exists naturally as monomer, dimer and polymers, there was a question concerning which of these is/are inhibitory form(s)."). Because the content

of the phrase complained of is also implicit in the remaining claim language, claim 18 is currently amended to omit "which is in a form," so as to expedite agreement as to allowable claims in this matter.

Claim 20 is also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. As discussed above, claim 20 is currently amended to omit the term "high affinity estrogen binding activity." Support for the limitation "having a greater E2 binding affinity than that of ERα or ERβ" is found in the specification in Example19, entitled *"A NEW HIGH ESTROGEN AFFINITY GROWTH REGULATING ESTROGEN RECEPTOR (ERγ),"* especially paragraph [0411], paragraph [0416] (*"The lowest K_d identified in a literature search was in the range 5 x 10^{-11} M to 1.0 x 10^{-10} M for the ERβ and 7 x 10^{-11} M to 1.1 x 10^{-10} M for the ERα."*), and paragraph [0417] "*Evidence is provided herein that all of the ER^+ cell lines analyzed in this presentation show estrogenic effects (i.e. positive growth responses significant to p <0.05 or P <0.01) obtained at 10 to more than 1000-fold lower E_2 concentrations than expected from the measurement of K_d, with these and related cell lines. It is proposed herein that estrogen promoted growth is mediated by an as yet to be characterized estrogen receptor designated ERγ.*").

Among the additional examples of support for this limitation in the specification and drawings, please see paragraph [0398] "*As shown in **Fig. 92**, a dose-response study demonstrated that in serum-free defined medium with 40 μg/mL of human plasma IgM, concentrations of 0.1 to 1.0 picomolar E_2 caused significant growth (p < 0.01).*"; paragraph [0399] *"Estrogen at as low as 0.1 picomolar caused more than one-half maximum growth response (**Fig. 97**)."*; and paragraph [0271] *"...the T47D and MTW9/PL2 cells grow significantly in response to 1.0 x 10^{-12} M E_2."* Clearly one of skill in the art would conclude from Applicant's disclosure that Applicant was in possession of the method claimed in claim 20, and sufficiently described the same.

Claim 82 is currently amended to more closely track the language in paragraph [0572] of the specification, *i.e.*, "vulnerability to breast cancer" instead of "DNA synthesis in breast tissue." This ground of rejection is now believed to be obviated.

Enablement - Claims 1-6, 17-19 (in part), 66, 67, 70, 73, 76, 81-86 and 89.

Claims 1-6, 17-19 (in part), 66, 67, 70, 73, 76, 81-86 and 89 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In the Office Action it is said that one of skill in the art would be subject to undue experimentation in order to make and use the claimed methods relying on correlating the levels of secretory immunoglobulins with the presence or susceptibility to steroid hormone responsive cancer. In reply, Applicant respectfully traverses this rejection. The methods of *Garde et al.* and *Gomez et al.* demonstrate the availability of known

techniques for measuring total IgA levels in plasma, serum and saliva, and describe "normal" ranges, including seasonal and cyclic variations, in a group of individuals. There appear to be no similar assessments of individuals with plasma IgA levels outside of the given ranges, and no indication of how any deviation from the stated ranges may reflect a disease state. It is well known that on the average dimeric IgA comprises about 10% of the total IgA in the blood. It is also known that the dimeric IgA in blood comes mostly from leakage from mucosal tissues, and that only a small fraction arises from other sites in the body (see paragraph [0496] of the Specification). It does not arise from peripheral blood B cells that make up 90% of the (monomeric) IgA in the blood. The artisan also knows that IgA in blood generally does not enter mucosal tissues from the blood. In accordance with the method of amended claim 1, measuring dimeric/polymeric IgA will provide an estimation of the status of the immune system that protects mucosal tissues from early cancers, which Applicant has disclosed correlates with mucosal cancer susceptibility.

In support of claim 1, Example 29 of Applicant's Specification describes how lowered levels of the immunoglobulin inhibitors can be assessed and correlated with predisposition to breast cancer. For example, paragraph [0494] describes *in vitro* testing of inhibitor in fluids and paragraph [0495] describes how *in vitro* test results are correlated with the *in vivo* condition of the individual, as follows:

> *The results are compared to similar tests using positive and negative control plasmas or serums, which have defined levels of IgA dimer and poly IgM. In this way the tumor cell growth inhibitory activity of the individual's plasma is measured. Because the in vitro assay system employs a cell line that forms breast or prostate tumors when implanted in vivo, the in vitro assay results are believed to be suggestive of the in vivo condition of the individual.*

Example 30 expands on IgA deficiency and its use as a measure of propensity to develop breast, prostate and other mucosal cancers. One of skill in the art would conclude that the need for ranges or levels of secretory immunoglobulins in plasma, for example, that are indicative of normal individuals versus individuals who are more susceptible to development of a steroid hormone responsive cancer (or versus individuals who are more susceptible to growth of such a cancer) are unnecessary when the direct assessment of inhibitory activity is carried out on the sample of fluid or secretion, in accordance with claims 1-6.

In paragraph [0400] of the Specification, and in Figures 98, 99, 101 and 102, for example, Applicant shows that dimeric/polymeric IgA levels over the concentration range of 2 μg/mL to 20 μg/mL are fully inhibitory, and that polymeric IgM is likewise inhibitory of steroid hormone responsive cell growth over the concentration range of 2-50 μg/mL. Furthermore, when armed with the

knowledge provided by Applicant's disclosure as to the inhibitory effect of dimeric/polymeric IgA and polymeric IgM, one of skill in the art could develop a set of dimeric/polymeric IgA measurements in fluid samples from a group of individuals and correlate those measurements to assay results (claim 4) obtained from the same samples, without undue experimentation. The particular cell lines (Table 1) employed in the disclosed assays were chosen because they grow similarly either *in vitro* or *in vivo*, and thus are models for predicting *in vivo* effects based on *in vitro* observations (also, see paragraphs [0215], [0230], [0280] and [0369] (*"Plainly, the serum-free conditions established herein are the most defined model assay systems yet established to demonstrate estrogen responsiveness in vitro."),* paragraph [0482] (*"The studies described hereinabove were performed in cell culture, and constitute the Phase I studies. That work employed well-established in vitro cell culture models recognized generally to yield physiologically relevant information."*), and paragraph [0284] (*"In every case, the effects of the various classes of steroid hormones on the different cell lines were consistent with their known tumor forming/growth properties in vivo or published responses in vitro."*). Therefore, the direct assessment or indirect assessment (new claim 94) of an amount of immunoglobulin inhibitor in a fluid sample, and an assessment of the ability of a like amount to inhibit or arrest cell growth in a model cell culture system (Example 1), would be considered by the artisan to be predictive to at least some extent of an *in vivo* effect of that quantity of inhibitor in the fluid sampled. Note that Applicant's results in cell culture models show that 14 days contact with dimeric IgA or polymeric IgM is enough to kill early ER+ breast cancer cells (see Example 21, especially paragraphs [0429] and [0430]).

By measuring the concentration of dimeric IgA, and finding this level well below average, one of skill in the art would conclude that monitoring (*e.g.* mammography) is more important for these women. Both ductal lavage and breast fluid aspiration are already in use clinically to seek abnormal cytology (see, *e.g.*, O'Shaughnessy JA, *et al* Ductal lavage and the clinical management of women at high risk for breast cancer. *Cancer* 94:292-298; and Wrensch MR *et al.* Breast cancer incidence in women with abnormal cytology in nipple aspirates of breast fluid. *Am J Epidemiol* 135:130141, 1991), so a person skilled in the art would recognize that the basic tools for carrying out Applicant's method of claim 1, to clinically measure dimeric IgA in breast fluid, for example, are already available. No undue experimentation would have been required of one of skill in the art at the time of Applicant's invention in order to measure the dimeric/polymeric IgA in the indicated body fluids and secretions to determine if they are abnormally low, in accordance with the methods of claims 1, 3, 89, for example. Also, since menstrual cycle data can be obtained at the time of sampling, and is routinely done clinically, the issue

of estrogen induced changes can be easily resolved and factored into the "normal" values of the immunoglobulin inhibitors without the need for undue experimentation.

Enablement - Claim 17

Claim 17 is amended to omit "absence of heterozygosity" as a possible condition, in favor of substituting "allelic imbalance of." This amendment is supported in the specification in Example 22, at paragraph [0444], for example, and also in Example 38 at paragraph [0532]. A recital of allelic imbalance avoids the possibility of conflicted directions in amended claim 17. Claims 18 and 19 are amended similarly to omit "loss of heterozygosity" and to insert "allelic imbalance," and to make their outcomes clearer.

Claim 17 is further amended to make the outcome clearer. This amendment is supported in the specification; for example at paragraph [0476] *"Early onset markers will be loss of immune surveillance without obligatory loss of TGFβ effects;"* and at paragraph [0478],

> *Conversion of normal cells to ER^+ responsive breast cancers involves the loss of expression of the TGFβ receptor system including one or more of the three different forms of the receptor. ... According to the presently proposed model, lesions in the TGFβ system precede lesions or other types of losses of the receptors for secretory immunoglobulins. The loss of TGFβ inhibitory responses may represent the earliest receptor change identifiable in estrogen responsive breast cancer. The view that early onset breast cancer is a failure in immune surveillance and not necessarily related to TGFβ provides a new focus for genetic screening and other diagnostic tools.*

Claim 17 is still further amended to require that the population of cells taken from the subject is capable of greater than one doubling *in vitro*. This amendment is supported in the Specification in paragraphs [0221]-[0222], [0266] *("These results graphically illustrate the hazards of interpreting 1.0 CPD responses either in favor of phenol red/contaminants as estrogens or in opposition to this proposal."),* [0379] (*"At concentrations of 20 to 50 μg/mL, IgM completely inhibited the growth of the MTW9/PL2 cells (i.e. < 1.0 CPD.)"*), and elsewhere throughout the Specification.

In the Office Action it is said that *"[g]iven the state of the art with respect to the inability of primary cells to grow in culture and the lack of teachings in the specification which address or remedy said problem, one of skill in the art would be subject to undue experimentation in order to use the claimed methods to detect loss of immunoglobulin regulation of cell growth... "* (page 10 of the Office Action). Applicant respectfully traverses and points to the teaching in the specification that the model cell culture systems mentioned above overcome material failings of the prior cell culture systems typically employed for demonstrating steroid hormone responsiveness. See, for example, paragraph [0237],

> *The MTW9/PL2 population is the first highly steroid hormone-responsive rat mammary tumor cell line to be established in culture from a carcinogen-induced tumor". As a direct consequence of the information provided above, this cell line is a unique and valuable asset for combination in vitro and in vivo modalities to be applied to clinically and commercially significant compounds or preparations and for the assay of the inhibitor content or hormone or anti-hormone activities.*

and paragraph [0238],

> *...As mentioned in the Background of the Invention, most existing rat mammary tumor cell lines are not suitable for use in evaluating hormone responsiveness in vivo because they are derived from outbred animals. This problem was overcome by developing the MTW9/PL2 rat mammary tumor cell line.*

Moreover, the above-mentioned amendment requiring more than one cell population doubling (CPD) obviates the concern expressed in the Office Action that primary cells might be unable to grow in culture, as cells that are essentially unable to exceed one CPD would not provide a satisfactory determination of the various conditions recited in claim 17. Further support for enablement of primary cell growth in Applicant's cell culture system is discussed below with respect to enablement of claims 7-15, 17-19, 68, 69, 72 and 79.

Enablement - Claims 7-15, 17-19, 68, 69, 72 and 79.

Claims 7-15, 17-19, 68, 69, 72 and 79 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office Action acknowledges that these claims are enabled for methods reliant upon the measurement of the ability of the poly-Ig receptor to mediate steroid hormone responsive cell growth in a specimen of mucosal epithelial cells wherein the cell specimen is a cultured cell line. However, the Office Action takes the position that the specification does not reasonably provide enablement for methods reliant upon such measurements wherein the specimen is taken from a patient. Applicant has obviated this ground of rejection with respect to claims 8, 13, 17, 18, 68 and 69 by currently amending those claims to require that any cell assays include cells that are capable of proliferating to the extent of more than one doubling. Support for such amendment is found in the Specification, previously mentioned with respect to the rejection of Claim 17.

With respect to claim 12, Applicant has disclosed more than one way to detect loss or impairment of negative regulation of breast tissue proliferation by the secretory immune system. One way is to test a sample of body fluid or secretion that contacts or is secreted by the breast tissue of the subject, to determine whether an inhibitory amount of the immunoglobulin inhibitors are present in the sample. These steps are set out in Claim 1, and its dependent claims, and also described in Example 29 of the Specification, for example. This method does not require the use of cells from the patient, but

instead, only a fluid sample or secretion, and thus fully enables claim 12. Another way to detect such loss or impairment is by *in vitro* testing of cells taken from the subject, as discussed above with respect to enablement of claim 17.

As to claims 7, 14 and 15 Applicant respectfully traverses this ground of rejection for at least the reason that the assaying and testing steps recited in those claims do not require proliferation of either primary cells or cells maintained in culture. The Specification enables these claims at paragraph [0472], for instance, which describes how ^{125}I-labeled IgA may be used to find the receptor on a cell and to assess its binding characteristics; and also in paragraph [0521], which describes how the receptor

> *...is preferably located and quantified by fluorescence immunohistochemistry after an appropriate fixation [citation] or by radioimmunoassay as described for other surface receptors [citation]. Monoclonal antibodies against the whole receptor or specific domains can also be used to quantify the receptor [citation]. A variety of new enzyme-linked immunosorbant assays (ELISA) are also available and can be applied at very high sensitivity based on biotin-avidin or chemiluminescence technology. The method to be applied will be dictated by the types of specimens supplied.*

Applicant submits that those methods, which do not require *in vitro* proliferation of primary cells from a patient, amply enable claims 7, 14 and 15, and obviate the present ground of rejection. Accordingly, Applicant's disclosure has described the claimed invention in such terms that one of skill in the art could carry out the methods of claims 7, 14 and 15 without undue experimentation.

Similar to claims 7, 14 and 15, claim 19 also does not require proliferation of either primary cells or cells maintained in culture in order to perform the determining steps. Support for the various steps of this claim are additionally found in the specification in Example 38, at [0532] and [0537], for example. Taken in view of the general knowledge in the art (*e.g.*, the wild-type poly IgR and Fcγ receptors and their genes are known), Applicant's disclosure amply shows that one of skill in the art would be able to carry out the method of claim 19 without undue experimentation.

Claim 79 also does not require proliferation of cells *in vitro* in order to carry out the claimed method. Accordingly, Applicant respectfully traverses the ground of rejection stated on page 9 of the Office Action as being non-applicable to claim 79.

Still further, Applicant disputes the Office Action's assessment of "*the state of the art with respect to the inability of primary cells to grow in culture,*" and Applicant traverses the position taken by the Office that Applicant's specification *"does not reasonably provide enablement for methods reliant upon measurement of the ability of the poly-Ig receptor to mediate steroid hormone responsive cell growth in a specimen of mucosal epithelial cells taken from a patient," i.e.*, primary cells. The

cited passage in the *Freshney* reference, dated 1994, does not reasonably reflect the state of the art at the time of Applicant's invention regarding culturing of primary cells, as evidenced by the technical journal articles and abstracts identified on the attached pages. Those articles and abstracts are submitted concurrently herewith in the form of a ***Supplemental Information Disclosure Statement.*** On the attached pages, numerous reports are identified which demonstrate the usefulness of serum-free defined conditions to grow epithelial cells from biopsy and other types of human cancer specimens, *i.e.*, primary cells. These representative examples are related to the cell types described in the present matter (*i.e.*, mucosal or epithelial), and demonstrate multiple cycles of cell division under serum-free conditions. A few of the articles have publication dates subsequent to the filing date of the instant patent application, and are included here for the purpose of showing that one of skill in the art would conclude that the serum-free culture of primary cells continues to be a viable technology, in contrast to the position taken by the Office.

The levels of *in vitro* primary cell growth reported in the above-mentioned journal articles and abstracts are within Applicant's required level of more than one cell division or population doubling *in vitro* (claims 5, 8, 13, 17, 18, 68, 69 and 71). In some of those reports the studies were terminated after one month, while in others the cells were propagated to eventually yield cell lines. Indeed, the published evidence indicates that serum free medium methods are applicable to most types of major mucosal origin cancers that are the subject of this patent application.

The above-mentioned reports are strong evidence of the widespread interest and application of *in vitro* culture of primary cells by a variety of investigators, and are contradictory to the Office's contention that "*primary cells taken from patients do not grow well in culture*" or that "*most of the cells, if not all of the cells [are not] able to propagate.*" Therefore, one of skill in the art would more likely conclude from Applicant's disclosure of the various model cell culture systems, which employ cells that are capable of growing either *in vivo* or *in vitro*, that Applicant's serum-free media will also support *in vitro* growth of a number of primary human cell types -- both normal and cancer cells, to the extent of more than one population doubling.

It should not be overlooked that Applicant has disclosed cell culture media compositions that overcome difficulties encountered with many of the prior-art serum free compositions. For instance, Applicants disclosure of conducting cell culture under conditions not recognized previously as very important, *i.e.*, restricted Fe(III) (claim 5) and the use of ferric iron chelators in the medium of hormone responsive cancer cells is a valuable advance. See Example 9, especially paragraph [0313] of the Specification.

Rejection Under 35 U.S.C. § 102(b) - Claims 20, 78 and 79.

Claims 20, 78 and 79 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 99/05171 (*Baron et al.*, previously referred to in the Office Action as *"Barton et al."*). It is said in the Office Action that the claimed estrogen-binding activity appears to be the same as the prior art ERβ_c receptor and isoforms thereof disclosed by *Baron et al.*, absent a showing of unobvious differences. In reply, Applicant traverses this rejection and points out that the claimed method is different than any method described by *Baron et al.*. The *Baron et al.* patent shows on its face (for example, at pages 48-50) that the ERβ-1 and ERβ-3 receptors to not have the requisite properties of Applicant's newly disclosed ERγ.

First it should be noted that the term "K_d" is generally accepted in the art to mean that the receptor is one-half saturated at the K_d concentration. It is also generally accepted that the association constant $K_\alpha = 1/K_d$ (see, for example, the attached excerpt from a standard textbook of biochemistry, TEXTBOOK OF BIOCHEMISTRY WITH CLINICAL CORRELATIONS, 5th ed., (2002) Thomas M. Devlin, Editor, Wiley-Liss, New York, New York, pp. 936-939). Thus, the larger the K_d, the less strong the ligand binding. Conversely, the smaller the K_d, the stronger the affinity of the ligand for the receptor. The *Baron et al.* patent contains a confusing misstatement at page 49, lines 22-24, where it is said with reference to Table I (page 50) that "the larger the number, the greater the affinity the estrogen has for the receptor." That may be a true statement when affinity is expressed as K_a, the association constant, but it is not a true statement when affinity is expressed as K_d values as in Table I of *Baron et al.* In Table I of *Baron et al.*, the properties of two isoforms of estrogen receptor beta (ERβ-1 and ERβ-3) are compared to the well known ERα. The reported K_d of 17β-estradiol for ERβ-3 is 7.14 nM, the K_d of 17β-estradiol for ERβ-1 is 0.57 nM, and the Kd of 17β-estradiol for ERα is 0.40 nM. Based on those values, the K_d of ERβ-3 is 17.85 times higher than that of the well characterized ERα. This means that ERβ-3 binds estrogen ligands less well than the ERα or ERβ-1. This is exactly opposite, however, to the position taken by the Office in reliance on *Baron et al.* Clearly, Table I of *Baron et al.* shows that 17 β estradiol has less affinity for both isoforms ERβ-1 and ERβ3 than for the ERα, when affinity is expressed in terms of K_d. By contrast, all of Applicant's data point to a new receptor with a much lower K_d (*i.e,*. much stronger estradiol binding characteristic) which binds estrogen at 10 to 100 times higher affinity than ERα.

In further distinction over the cited reference, one of skill in the art would readily recognize in *Baron et al.* that the specific activity of the labeled ligand (in the nanomolar concentration range) is not

sufficiently high to measure binding at the low picomolar levels taught by Applicant. The data of *Baron et al.* show that neither the ERβ-1 nor the new isoform ERβ-3 have the affinity constants necessary to explain Applicant's disclosed cell growth effects at low picomolar concentrations (see Applicant's specification at paragraph [0417], for example). Applicant disclosed growth responsive estradiol binding affinity, expressed in terms of K_d, of less than 1.0×10^{-11} M. This is more than a 700 fold lower estrogen concentration than the estradiol binding affinity (Kd) of *Baron et al.* Thus, one of skill in the art would reasonably conclude that there is simply no way that *Baron et al.*'s ERβ-3 modulates the same growth effects Applicant has ascribed to a new ERγ receptor.

It should also be noted that there is no teaching in the *Baron et al.* patent that relates the ERβ-3 to growth regulation, especially to the growth of all of the target cell types and species examined and disclosed by Applicant. In fact, *Baron et al.* describes ERβ-3 as a negative modulator of the effects of other receptors (page 51, line 28 of *Baron et al.*). *Baron et al.* do not teach ascertaining whether their ERβ isoforms are present in a mucosal epithelial cancer cell, and do not teach that the presence of an ERβ isoform in such a cancer cell is an indicator of whether that cell is estrogen dependent for growth. As a consequence, there can be no teaching by the cited reference as to whether an anti-estrogen based therapy is indicated or contra-indicated for a certain mucosal epithelial tissue. For at least these reasons, the method of claims 20, 78 and 79 distinguish over *Baron et al.*

Additional Amendments

Any current amendments to the claims which are not specifically discussed above are made for reasons other than patentability. For example, to improve the claim form and readability, to use terminology that is believed to be more consistent with wording in the specification or with other claims, or to ensure coverage of specific embodiments to which Applicant is entitled. Each new claim is properly included with the claims of the elected Restriction Group.

New claims 91 and 92 depend from claims 8 and 13, respectively, and expressly require that the detected receptor is the known poly-Ig receptor. See paragraphs [0200] and [0464] of the Specification, where this limitation is supported.

New claim 93 depends from claim 20 and includes a limitation that further distinguishes over the *Baron et al.* reference. Support for this claim is found at paragraph [0004], [0512] and elsewhere in the Specification.

New claim 94, which depends from claim 1, is supported in the specification at paragraph [0492] and elsewhere in the Specification. For example, the "J chain" component of dimeric/polymeric IgA and polymeric IgM and the term "secretory component" are defined in paragraphs [0003] and

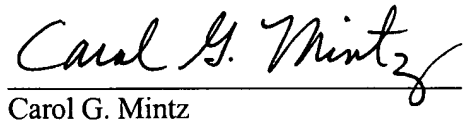
[0004]. This claim demonstrates indirect ways in which the sufficiency or insufficiency of immunoglobulin inhibition of steroid hormone responsive cell growth may be clinically assessed. New claim 94 better ensures coverage of certain embodiments to which Applicant is entitled.

Conclusion

Applicant believes that this is a full and complete response to each rejection, objection and requirement. If any item has been overlooked, the opportunity to supplement this response is respectfully requested. Applicant may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future.

Applicant respectfully requests reconsideration of this application and allowance of all claims. If any issues remain in controversy, Applicant respectfully requests a telephonic Examiner Interview to facilitate the resolution of such matters. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,



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AGENT FOR APPLICANT